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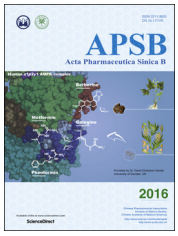

ORIGINAL ARTICLE

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

Wei Xu[a,b], Garth Boehm[b,*], Qiang Zheng[b,c,]**

[a]*School of Pharmaceutical Sciences, Peking University, Beijing 100871, China*
[b]*Center for Pharmaceutical Information and Engineering Research, Peking University, Beijing 100871, China*
[c]*Department of Industrial Engineering and Management, College of Engineering, Peking University, Beijing 100871, China*

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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.

*Corresponding author.
**Corresponding author at: Department of Industrial Engineering and Management, College of Engineering, Peking University, Beijing 100871, China.
E-mail addresses: garth.boehm@gmail.com (Garth Boehm), zhengqiang@pku.edu.cn (Qiang Zheng).

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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[1].

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[2] and top oral drugs in countries worldwide[3,4]. 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[5,6]. 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[7–9]. 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[8–11]. The government procures the supply of EML products and provides them to health-care institutions[10,11]. 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[11,12]. 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[13] contains 317 chemical and biological drug products of a total of 520 where the other products are traditional Chinese medicines (TCMs)[(1)]. 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[14,15].

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[16] 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[17] and Drug Recalls[18]. ADE data is massive[19] 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[20]. 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[21] 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[22].

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

[(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.

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[23–25] 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[26] 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

Table 1 Recalls eliminated from the original list.

Eliminated class of recall	No.	Recall reason given on FDA website	Reason for elimination
Contain ingredients without an approved ANDA/NDA	241	• Marketed without an ANDA/NDA (225) • CGMP deviations (10) • Misbranded(6)	The products in question were not approved by FDA
Compounding failures	1770	• Lack assurance of sterility (610) • Penicillin cross contamination (850) • Methylprednisolone compounding failure (298) • CGMP deviations (10) • Chemical contamination (1) • Microbial contamination (1)	The products in question were not approved by FDA. These compounding pharmacies do not (or should not) provide drug product for sale under normal commercial conditions
Penicillin cross contamination due to non-compounding failures	5	• Penicillin cross contamination (5)	Any product can become cross contaminated. It is a facility or procedure issue which has nothing to do with the particular product.
Due to reasons couldn't be decided according to the given information	522	• Microbial contamination (260) • Subpotent (59) • Impurities/degradation (49) • Presence of particulate matter (40) • Contraceptive tablets out of sequence (23) • Failed dissolution specifications (21) • Lack assurance of sterility (17) • Discoloration (13) • CGMP deviations (8) • Misbranded (8) • Superpotent (7) • Presence of precipitate (3) • Failed content uniformity requirements (3) • Failed tablets/capsules specifications (3) • Does not meet monograph (2) • Failed PH specifications (2) • Does not deliver proper metered dose (2) • Defective delivery system (1) • Due to an abundance of caution (1)	The cited reason on FDA website were too vague to determine anything about the underlying reason for the recall

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. The methods are entirely directed at stress testing for analytical method development. 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) • Presence of foreign substances/ particulate matter (81) • Lack assurance of sterility (66) • Adulterated presence of foreign tablets/capsules (41) • Defective container/container leakage (33) • CGMP deviations (28) • Miscalibrated/defective delivery system (7) • Short fill (6) • Unit dose mispackaging (4) • Superpotent (4) • Does not deliver proper metered dose (2) • Impurities/degradation (2) • Discoloration (1)	Stability failures	274	• Impurities/degradation (82) • Subpotent (67) • Failed dissolution specifications (50) • Stability data doesn't support expiration date (24) • Product lacks stability/failed stability specifications (18) • CGMP deviations (15) • Presence of particulate matter (6) • Lack assurance of sterility (6) • Failed pH specifications (2) • Microbial contamination (1) • Superpotent (1) • Failed moisture limit (1) • Failed tablets/capsules specifications (1)
CGMP failures	331	• CGMP deviations (297) • Lack assurance of sterility (18) • Impurities/degradation (4) • Microbial contamination (3) • Subpotent (3) • Superpotent (2) • Using materials not listed in FDA application (2) • Failed dissolution specifications (1) • Incorrect product formulation (1)	Manufacturing failures	224	• Presence of foreign substances/particulate matter (73) • Failed tablets/capsules specifications (44) • Miscalibrated/defective delivery system (22) • Failed content uniformity specifications (19) • Superpotent (18) • Subpotent (12) • Cross contamination/other products discoloration (11) • Presence of precipitate (8) • Resuspension problems (5)
Contamination	174	• Microbial contamination (93) • Chemical contamination (57) • Lack assurance of sterility (13) • Cross contamination (9) • Oversulfated chondroitin sulfate (2)			• Crystallization (4) • Tablet/capsules imprinted with wrong ID (4) • Does not deliver proper metered dose (1) • Defective product (1) • 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			140
Presence of foreign substances		72		72
Dissolution	52			52
Tablet weight		50		50
Content uniformity	4	13		17
Peel force failure		12		12
Cross contamination/other products discoloration		11		11
Subpotent		10		10
API precipatate		9		9
Presence of particulate matter	6	3		9
Failed stability specifications	8			8
Superpotent	1	7		8
Adhesion failure		6		6
CGMP deviations	5			5
Impurity			4	4
Leaking capsules		4		4
Crystallization		4		4
Friability		4		4
Logo incorrect		4		4
Particle size	4			4
AET failure	3			3
Viscosity	3			3
Microbal contamination	2			2
Packaging	2			2
PE failure	2			2
Sterility	1	1		2
Failed pH specification	2			2
Logo illegible		1		1
Failed unit weight	1			1
Failed unit weight/osmalaity	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	Ethambutol 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	Phenytoin 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

Table 5 Stability indicating methodology literature search summary.

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	2.5 mg lorazepam: 40 °C for 15 days, with blister	2.5 mg lorazepam: 40 °C for 15 days, without blister	/
Levothyroxine sodium	[29]	HPLC	Storage condition 1: 60 °C, 0% RH, 20.9% O_2 Storage condition 2: 60 °C, 75% RH, 20.9% O_2 Storage condition 3: 60 °C, 0% RH, 0% O_2	Storage condition 4: RT, 0% RH, 20.9% O_2 Storage condition 5: RT, 75% RH, 20.9% O_2 Storage condition 6: RT, 0% RH, 0% O_2	/	/	/
	[30]	HPLC	Stability of pentahydrate Form: 25 °C/0% RH; 40 °C/ 0% RH; 25 °C/60% RH; 40 °C /75%RH	Stability of dehydrated Form: 25 °C/0% RH and 40 °C/0%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 ± 1 °C.	/	/
	[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 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.	Stability with different diluents: manufactured with 4 diluents and/or dibasic calcium phosphate.	Stability with pH modifiers: manufactured with dibasic calcium phosphate and different basic pH modifiers and acidic 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% H_2O_2, 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% H_2O_2, 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/m^2 in UV light and 1.2 million lx·h in visible light for 36 h (26.62% degradation).

Table 5 (*continued*)

Drug product	Ref.	Stability indicating method	Stability testing method				
			Acid hydrolysis	Alkali hydrolysis	Oxidative degradation	Thermal degradation	Photolytic degradation
	[34]	HPLC	25 mg RSP, 10 mL of 5 mol/L HCl, 10 h on water bath	25 mg RSP, 10 mL 5 mol/L NaOH, 10 h on water bath	25 mg RSP, 3.5 mL of 3% H_2O_2, 5 min at ambient temperature (11.0% degradation)	25 mg RSP, 72 h at 105 °C	25 mg RSP, kept in a photolytic chamber at 1.2 million/h
Oxytocin (OT)	[35]	HPLC	0.02 U/mL OT in 1 mol/L HCl and heated at 90 °C for 1 h	0.02 U/mL OT in 1 mol/L NaOH and heated at 90 °C for 1 h	/	/	/
	[36]	HPLC	20 h (29.8% degradation)	20 h (13.3% degradation)	16 h (20.0% degradation)	105 °C, 5 h (22.2% degradation)	500-700 ft-candles, 48 h (0.0% degradation)
	[37]	HPLC	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.	A 2 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.	A 2 mL of a 3% H_2O_2 solution was added to 8 ml of a 10 IU/mL solution of OT. This solution was placed in a dark locker for 2 h.	A 10 IU/mL OT solution was heated to and maintained at 50 °C for 10 min.	A 10 mL OT solution at a concentration of 10 IU/mL was exposed to natural sunlight for 8 h.
Amlodipine besylate (AML)	[38]	RP-HPLC	1 mol/L HCl, in a water bath at 105 °C for 30 min (Recovery: 64.32%)	2 mol/L NaOH, in a water bath at 105 °C for 90 min (Recovery: 78.31%)	10% H_2O_2, in a water bath 105 °C for 45 min (Recovery: 32.58%)	Drugs were kept in a hot air oven at 100 °C for 48 h	Drugs were exposed to 254 nm and 366 nm of ultraviolet light for 48 h
	[39]	RP-HPLC	0.1 mol/L HCl, in a water bath at 80 °C for 1 h. (Recovery: 96.36%)	0.1 mol/L NaOH, in a water bath at 80 °C for 1 h (Recovery: 16.55%)	3% H_2O_2, in a water bath at 80 °C for 1 h (Recovery: 97.51%)	Solid drugs were exposed in oven at 80 °C for 2 h. (Recovery: 94.62)	/
	[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 mol/L NaOH, in a water bath at 60 °C for 10 min (Degradation 35%)	5% H_2O_2, in a water bath at 80 °C for 2 h (Degradation 25%)	100 mg AML was kept in an oven at 90 °C for 18 h (No degradation)	100 mg AML was subjected to UV irradation at 254 nm for 60 h (No degradation)
	[42]	HPTLC	Using 9 mL of AML solutions and 0.5 mL of 5 mol/L HCl and keeping it overnight (0.1 mol/L HCl, negligible; 5 mol/L HCl 48.93% 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 NaOH, 42.10% decrease in peak area)	Using 9 mL of AML solutions and 0.5 mL of 30% H_2O_2 and keeping at room temperature for 72 h (3% hydrogen peroxide, negligible; 30 hydrogen peroxide, 10.74 decrease in peak area)	The standard drug in solid form was placed in oven at 80 °C for 24 h. (Less than 1%)	Exposing the bulk drug to UV light 200 Wh/m^2 followed by Cool Fluorescent light up to illumination of 1.2 million Lx·h (Less than 2%)
Famotidine	[43]	RP-HPLC	To 0.49 mL of famotidine stock	To 0.49 mL of famotidine stock	To 0.49 mL of famotidine stock	To 0.49 mL of famotidine stock	/

			solution 3 mL of 0.1 mol/L HCl was added and kept at normal condition for 90 min (1.51% degradation)	solution 3 mL of 0.1 mol/L NaOH was added and kept at normal conditions for 90 min (1.28% degradation)	solution 1 mL of 3% *w/v* H_2O_2 was added (1.49% degradation)	solution 3 mL of the dilute was added and kept at a reflex condiction for 60 minutes (1.19% degradation)	
	[44]	RP-HPLC	0.1 mol/L HCl for 24 h at TR (6.56% degradation)	0.1 mol/L NaOH for 24 h at RT (8.58% degradation)	1% H_2O_2 for 24 h at TR (18.63% degradation)	45 °C for 36 h (11.60% degradation)	Exposed in the presence of light (14.61% degradation)
	[45]	RP-HPLC	(97.46%)	(peak distorted)	(104.32%)	/	(94.08%)
	[46]	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)	The drug (10 mg) was dissolved in 10 mL of 1 mol/L NaOH solution and kept for 8 h at RT in dark. (86.05 ± 5.39% Recovery)	10 mg drug was dissolved in 10 mL of methanolic solution of H_2O_2 (10%, *v/v*) and kept for 8 h at RT in the dark. (75.34 ± 11.08% Recovery)	The powdered drug was stored for 3 h at 55 °C (93.79 ± 10.72% Recovery)	Drug solution was exposed to direct sunlight for 3 days (GMT, 09:00-17:00 h at 30 °C, total 24 h) (71.70 ± 7.65% Recovery)
	[47]	HPLC	0.1 mol/L HCl, for 20 min	0.1 mol/L NaOH for 20 min	/	/	/
Fluocinonide	[48]	LC	1 mol/L HCl, 48 h (86.5% of active substances)	0.1 mol/L NaOH, 30 min (74.7% of active substances)	5% H_2O_2, 48 h (90.8% of active substances)	60 °C, 10 days (99.3% of active substances)	carried out as per ICH Q1B, 10 days (99.2% of active substances)
Amoxicillin	[49]	LC	to 15 mL of 10 μg/mL solution, 15 mL of 1 mol/L HCl was added and heated for 2 h at 70 °C (20%-25% degradation)	to 15 mL of 10 μg/mL solution, 15 mL of 0.05 mol/L NaOH was added and heated for 2 h at 70 °C (15%-20% degradation)	to 15 mL of 10 μg/mL solution, 15 mL of 20% H_2O_2 was added and heated for 2 h at 70 °C (5%-7% degradation)	/	15 mL of 10 μg/mL solution was exposed to artificial white light (12,000 lx for 144 h, at 25 °C) and UV light (254 nm for 3 h) (5%-7% degradation)
	[50]	HPLC	0.5 mol/L HCl (6.65% degradation)	0.1 mol/L NaOH (6.21% degradation)	0.1% (*v/v*) H_2O_2 (5.01% degradation)	(13.12% degradation)	(8.59% degradation)

/, not applicable.

Table 6 Summary of product recalls by dosage forms due to stability caused impurities/degradation/subpotent and stability caused dissolution failures.

Administration route	Dosage from	No.
Stability caused impurities/degradation/subpotent (a)		
Oral	Tablet	73
	Solution	9
	Extended-release capsule	6
	Capsule	4
	Extended-release tablet	1
	Delayed-release capsule	1
	Chewable tablet	1
	Suspension	1
	Total	97
Parenteral	Injection	24
	Total	24
Topical	Ointment	4
	Lotion	2
	Cream	2
	Solution	2
	Gel	1
	Total	11
Others	Ophthalmic solution	3
	Otic solution	2
	Suppository	2
	Inhalation solution	1
	Total	8
Stability caused dissolution failures (b)		
Oral	Extended-release tablet	20
	Tablet	14
	Extended-release capsule	10
	Delayed-release capsule	2
	Suspension	2
	Delayed-release tablet	2
	Transmucosal	1
	Total	51
Topical	Transdermal system	1
	Total	1

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 (6.45%) are tablets and 2 (6.45%) 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 gleamed 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

[(2)] (34/0.089)/(34/0.089+14/0.911) × 100%=96%.

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

Dosage form	Total	After exclusion[a]	Percentage (%)
Oral solid ordinary	202,145,656	187,683,992[b]	92.85%
Oral solid long-acting	18,170,650	18,122,975[c]	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.
[a]Products not identify dosage form, whether it is a drug or otherwise not relevant were excluded.
[b,c]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	2,55
Metformin hydrochloride	1000	D-1113-2012	Tablet	Generic	100–300 (very high)	Very high	2,56
	850	D-1114-2012	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
Ibuprofen	200	D-1216-2012	Tablet	Brand	0.01–0.05 (low)	High	2,61

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 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	Generic
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

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.

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