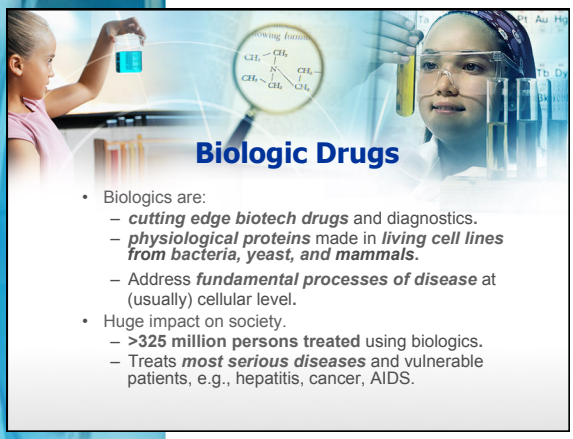

Biosimilars: Status, Oversight, and Commercialization
Bryan A. Liang, MD, PhD, JD , UCSD School of Medicine,
San Diego Center for Patient Safety


Biologic Drugs
• Biologics are:
– cutting edge biotech drugs and diagnostics.
– physiological proteins made in living cell lines from bacteria, yeast, and mammals.
– Address fundamental processes of disease at (usually) cellular level.
• Huge impact on society.
– >325 million persons treated using biologics.
– Treats most serious diseases and vulnerable patients, e.g., hepatitis, cancer, AIDS.


But …
• Biologics represent a huge healthcare cost.
– can reach >$100,000 in treatment costs annually.
– global market growing at least twice as fast as that for small molecule drugs.
– comprises ~15-20% of total pharmaceutical sales.
– represents nearly 1/3 of the global development pipeline.
– 2016: 7/10 top pharmaceuticals globally will be biologics,
• Top five Medicare Part B drugs administered in physician offices are biologics.
• Top drug—erythropoeitin—$2 billion.
• Greater than entire budget of FDA.

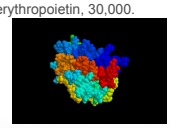
So …

Advent of Biosimilars/Follow On Biologics

- ***Key Question: Can we make cheap copies of branded biologics, i.e., biosimilars?***
- Look at ***science of biologics.***
  - **Assess complexity: Size; Manufacturing**
  - **Assess safety issues: Immunogenicity; Excipients**
- Look at ***extant regulation of biosimilars approval.***
  - **USA Biologics Price Competition and Innovation Act**
  - **EU Biosimilars System**
- Look at ***market status for biosimilars.***

Complexity: Size

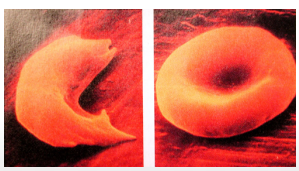
- Biologics (injectables) much more complex than chemical medicines (pills).
  - **Molecular size:**
    - E.g., aspirin: 180; erythropoietin, 30,000.



  - **Chemical medicines *completely characterized* by molecular formula ($C_9H_8O_4$); biologics *only approximated* at best (1˚, 2˚, 3˚, and sometimes 4˚)**

Complexity: Size Impact

- Tiny changes in protein can have devastating results, e.g., sickle cell anemia (one amino acid).



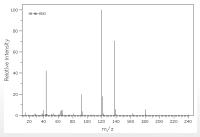
Complexity: Mfg'ing

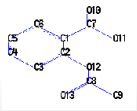
- **Much more complex** manufacturing.
  - **e.g., quality tests: 40-50 versus 200-300.**

- ***"Swirling flasks" versus growing organisms.***

Complexity: Mfg'ing

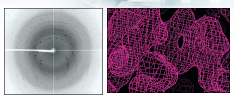
- ***Chemical medicines*** can be ***copied identically***—**generics**.
  - **Atom by atom chemical formula comparisons and bioequivalence testing.**
  - ***Homogeneous* material *perfectly characterized*** due to **small size** and relatively **simple structure.**

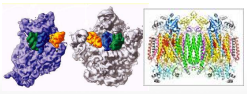




Complexity: Mfg'ing

- Biologics can *never* be copied identically.
  - Like humans, ***diversity* of living organisms** create **variation**—actual biosimilar product, side products, nascent cell proteins.
  - **Biologic biosimilar "product"** actually ***heterogeneous* mix imperfectly characterized** by shape and gross geometry due to immensity.





Compexity: Mfg'ing

- ***Exquisite sensitivity*** of biologic manufacturing:
  - **PK/PD characteristics *change*** moving manufacturing **from one site to another**.
  - Most **discovered issues were in *cooperative* licensing** technology transfer and use for a branded product.
  - ***Biosimilars are NOT manufactured under cooperative licensing between competitors!***

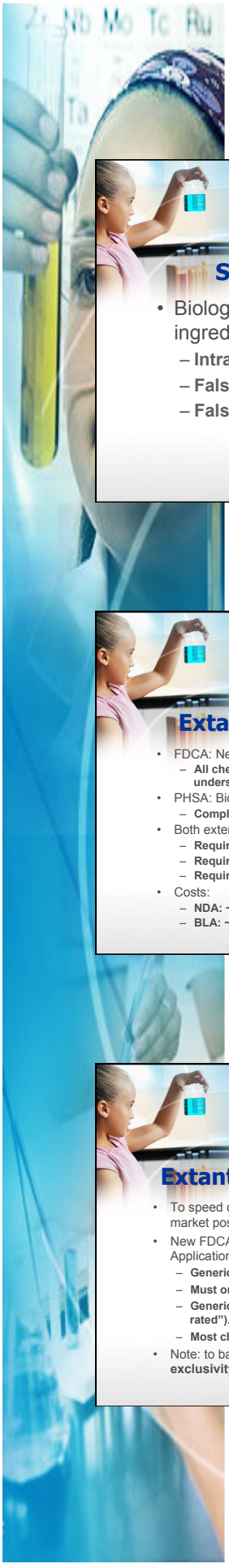
Safety: Immunogenicity

- **Chemical drug tiny size** generally does ***not*** induce body immune response.
- **Biologics large size** associated with ***immunologic* reactions**.
  - **Some responses are good: vaccines.**
  - **Unwanted immunogenicity responses can be devastating/life threatening.**

Immunogenicity *very* hard to predict for all biologics – branded and biosimilars.

Safety: Illustration-Eprex

- **Epogen/Eprex** (erythropoietin) made by Amgen and J&J using same "recipe."
- Amgen product in US; J&J in EU.
- 1998, **J&J makes "minor" change** in **product manufacturing** (replacing inert stabilizing agent and packaging).
- 2000, **hundreds of EU reports of pure red cell aplasia** (0 reports in US).
  - **PRCA: body stops creating red blood cells.**
  - **Patients die; those alive found to have allergic immunogenicity reaction to Eprex.**
  - **Patients found to be allergic to *all* erythropoietins, *including* body's own.**
- From first report to present, **hundreds of scientists researching cause**.
- **Current (debated) explanation: stabilizing agent interacted with rubber stopper.**



Safety: Excipients

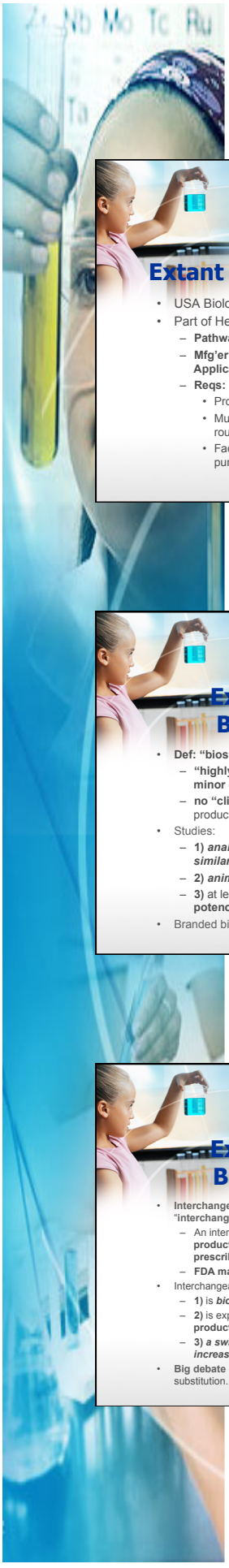
- Biologic excipient (non-active ingredient) reactions.
  - **Intravascular hemolysis.**
  - **False elevated glucose.**
  - **False negative hepatitis B results.**

Extant Regulation-New Drugs

- FDCA: New Drug Application (NDA).
  - **All chemical and some "simple, relatively small, well understood biologic" drugs.**
- PHSA: Biological License Application (BLA).
  - **Complex biologics, e.g., monoclonal antibodies, vaccines.**
- Both extensive before marketing approval given:
  - **Require *preclinical* studies showing PK and PD info.**
  - **Requires *clinical* studies showing safety and efficacy.**
  - **Requires demonstration of *good manufacturing practices*.**
- Costs:
  - **NDA: ~$800 million.**
  - **BLA: ~$1.2 billion.**

Extant Regulation-Generics

- To speed cheaper generic versions of **chemical** drugs to market post-patent expiry, Hatch-Waxman Act passed in 1984.
- New FDCA §505(j)—created ANDA: Abbreviated New Drug Application.
  - **Generic firms can rely on *originator safety and efficacy data*.**
  - **Must only show *chemical equivalence and bioequivalence*.**
  - **Generics will be *substitutable* for originator drugs ("AB rated").**
  - **Most chemical generics go through this process.**
- Note: to balance, **brand name companies get 5 years data exclusivity**.



Extant Regulation-Biosimilars

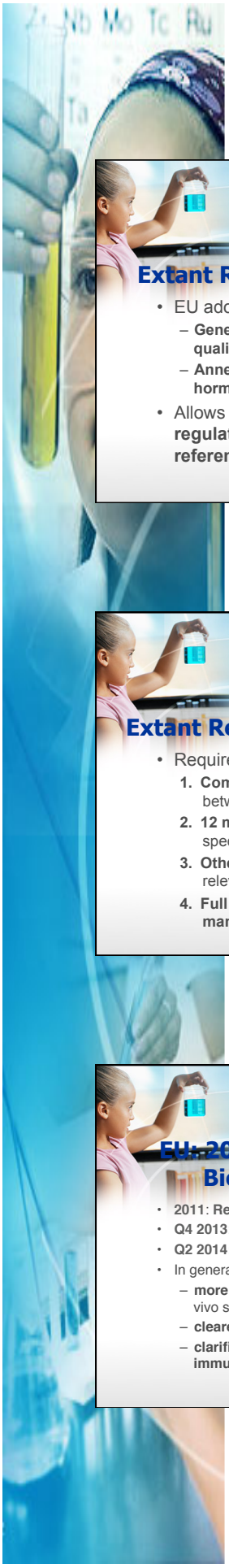
- USA Biologics Price Competition and Innovation Act (BPCIA).
- Part of Healthcare Reform bill (ACA).
  - **Pathway for biosimilars approval.**
  - **Mfg'er may submit a Biosimilar Biological Product Application (BBPA).**
  - **Reqs:**
    - Product **must be "biosimilar"** to a single reference product.
    - Must **share same MURDS characteristics:** mechanism, use, route of administration, dosage form and strength.
    - Facility that manufactures the biosimilar must meet safety and purity standards [**cGMP**].

Extant Regulation-Biosimlars (cont.)

- **Def: "biosimilar" product:**
  - **"highly similar to the reference product notwithstanding minor differences in clinically inactive components"** and
  - **no "clinically meaningful differences"** between the two products**.**
- Studies:
  - **1) *analytical studies* demonstrating** the high degree of ***similarity*;**
  - **2) *animal studies*,** including ***toxicity* assessments, and**
  - **3)** at least one ***clinical study* demonstrating safety, purity and potency.**
- Branded biologics given **12 years data exclusivity**.

Extant Regulation-Biosimilars (cont.)

- **Interchangeability**: a biosimilar filer may also show proposed product is "**interchangeable**" with reference product (no EU equivalent).
  - An interchangeable product **"may be substituted for the reference product *without* the intervention of the healthcare provider who prescribed the reference product."**
  - **FDA may award first** interchangeable product **market exclusivity.**
- Interchangeability requires product:
  - **1)** is ***biosimilar,***
  - **2)** is expected to ***produce the same clinical result* as reference product, and**
  - **3) *a switch or alternation between products will not pose an increased risk*** *in terms of safety or efficacy.*
- **Big debate on whether pharmacists must notify prescribing MD** of substitution.



Extant Regulation-EU Biosimilars

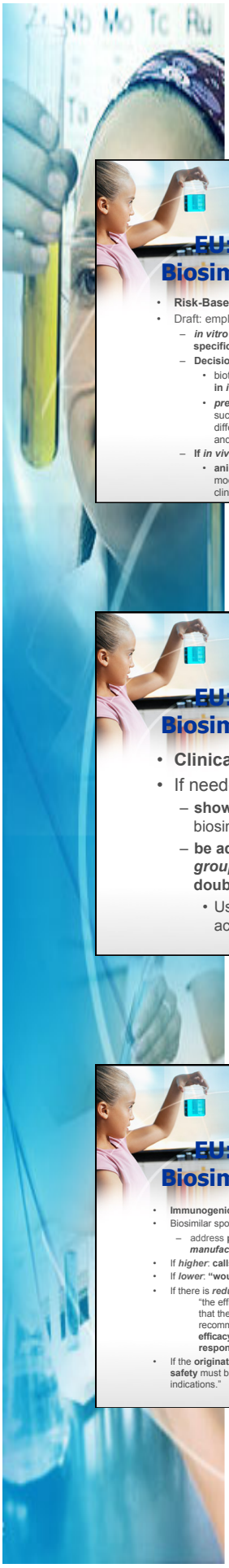
- EU adopted biosimilars regulation in 2004.
  - **General: clinical/nonclinical requirements and quality requirements.**
  - **Annex guidance: on insulin, human growth hormone, erythropoeitin, G-CSF, etc..**
- Allows biosimilar applicant reliance upon **regulator knowledge of originator/ reference molecule safety and efficacy**.

Extant Regulation-EU Biosimilars

- Requires ***clinical trials*** to show:
  1. **Comparability and clinical differences** between biosimilar and reference drug**.**
  2. **12 months of immunogenicity data** with specified populations.
  3. **Other clinical studies** if requested and relevant.
  4. **Full pharmacovigilance and risk management plan.**

EU: 2011, 2013/2014 Draft Biosimilar Revisions

- **2011**: **Revisions begin** for EU biosimilars regulation.
- **Q4 2013**: **Final recommendations due** after comments.
- **Q2 2014: Final review and revisions**.
- In general: European Medicines Agency recommends:
  - **more risk-based studies** to determine need for in vivo studies;
  - **clearer guidance** on **clinical trials**, and
  - **clarification** on addressing biosimilar v. originator **immunogenicity**.



EU: 2011, 2013 Draft Biosimilar Revisions (cont.)

- **Risk-Based Studies**
- Draft: employ *risk-based approach to non-clinical biosimilar review*.
  - ***in vitro* studies should be conducted first, and on its basis determine specific *in vivo* work needed.**
  - **Decision to proceed to *in vivo* studies should take account:**
    - biotech-derived drugs may have ***in vivo* effects not fully elucidated in *in vitro*** studies;
    - ***presence of quality issues* not detected in the reference product** such as new post-translational *modification* structures; significant; differences in *quality attributes* between reference drug and biosimilar; and/or relevant differences in *formulation*.
  - **If *in vivo* studies are deemed necessary:**
    - **animal species or other model** should be considered, unless such a model is not available, in which case the product should be taken to clinical trials for pK and pD studies.

EU: 2011, 2013 Draft Biosimilar Revisions (cont.)

- **Clinical Trials.**
- If needed, must:
  - **show *comparable clinical efficacy*** of the biosimilar and reference drug;
  - **be adequately powered, randomized, *parallel-group comparative clinical trials*, preferably double-blind.**
    - Use of non-inferiority design may be acceptable if "justified."

EU: 2011, 2013 Draft Biosimilar Revisions (cont.)

- **Immunogenicity.**
- Biosimilar sponsors must:
  - address **possible *immunogenicity potentially arising from different manufacturing process*** cf. reference drug.
- If ***higher***: **calls the product's biosimilarity into question**.
- If ***lower***: **"would not preclude approval as a biosimilar"**.
- If there is ***reduced development of neutralizing antibodies with the biosimilar***, "the efficacy analysis of the entire study population could erroneously suggest that the biosimilar is more efficacious than the reference product. It is therefore recommended to **pre-specify an additional exploratory subgroup analysis of efficacy and safety in those patients that did not mount an anti-drug antibody response during the clinical trial**."
- If the **originator has more than one indication**, then the **biosimilar's efficacy and safety** must be "justified, or if necessary demonstrated, ***for each*** of the claimed indications."

Policy Foundational Concerns

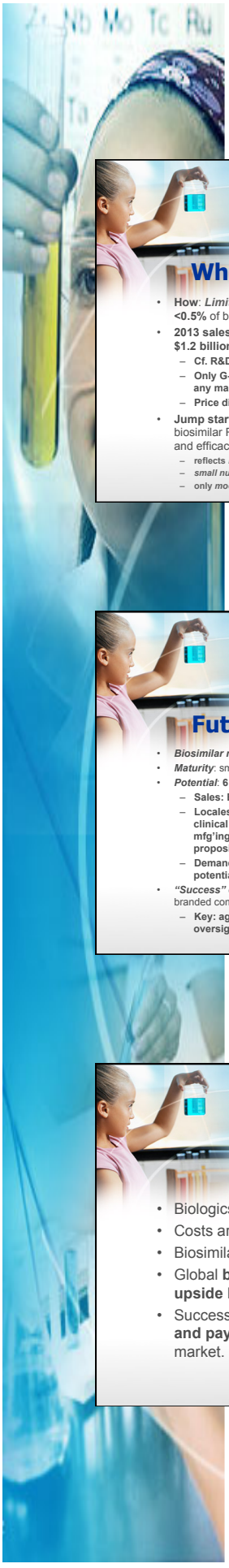
- Information gaps?
  - ***Large gaps in science-based characterization:*** complex biologics and *prediction of safety* issues difficult.
- Populations at risk?
  - ***Socially vulnerable*:** needing cheapest price (uninsured/ACA gaps), medically vulnerable—cancer, AIDS patients.
- Potential Harm?
  - ***High severity*:** life-threatening adverse events, e.g., immunogenicity.
- Policy philosophy: "Higher and Greater": info gaps, vulnerable patients, and potential harm means **err on side of safety**.

Who, What, and How?

- **Who**: ***global pharmerging market*** players (BRICS countries).
- **Other Markets**: ***frontier markets*** (MINT markets).
- **Companies**: Merck [bio-betters]; Merck-Serono; Boehringer Ingelheim; Samsung-Biogen-Idec; Pfizer; Amgen-Actavis; Novartis-Sandoz; Celltrion-Hospira; Teva-Cephalon; plus more every day.
  - **cf. the "anti-biosimilars company": Roche.**

Who, What, and How? (cont.)

- **What**: generally mAbs (Herceptin/trastuzumab; Rituxan/rituximab; Remicade/infliximab)
- 2012:
  - **73 mAbs under development.**
    - ~30 companies working on trastuzumab (Herceptin) alone – EU patent expiry 2014 (USA 2019).
  - **59 preclinical stage; 5 in Phase I/II; 9 in Phase III**
- Current record of biosimilar applications in EU.
  - **7 in 2012 cf. 0 in 2011, 0 in 2010, 1 in 2009 [total approved 2004-2013: 15].**
- 2013: **First EU biosimilar mAb** approved: Inflectra/Remsima by Hospira/Celltrion (infliximab; biosimilar of Remicade by J&J).
- 2013: First **Indian "similar biologics" mAbs** approved: Hertraz/CanMAb (biosimilar of Herceptin by Mylan/Biocon); Mabtas (biosimilar of Rituxan by Intas).



Who, What, and How?

- **How**: ***Limited commercialization success***: biosimilars represent **<0.5%** of biotech drug spending in developed markets.
- **2013 sales ~$1.1-1.2 billion**; **cumulative sales from 2006-2011 ~ $1.2 billion**
  - **Cf. R&D, manufacturing costs of $1-1.5 billion per biosimilar.**
  - **Only G-CSF/neupogen biosimilars have in total >50% penetration in any market.**
  - **Price discounting ~20% (cf. small molecule generics at ~90%).**
- **Jump start efforts**: e.g., Norway: will ***fund clinical studies*** for biosimilar Remicade versions (Inflectra) ***to reassure MDs*** of safety and efficacy.
  - **reflects *high caution among MDs* across countries,**
  - ***small number of* manufacturers across products, and**
  - **only *modest price discounts.***

Future Considerations

- ***Biosimilar market***: will **grow** to between $2-22 Billion/annually.
- ***Maturity***: small molecule generics took **>10 years** to be accepted.
- ***Potential***: **6 largest mAbs off patent by 2019**.
  - **Sales: E.g., Remicade/infliximab - $6 billion alone; ~$60 billion total.**
  - **Locales: Emerging/Frontier Markets: *both* producers and consumers; clinical trials locales (e.g., Colombia and South Korea marketing and mfg'ing approval for infliximab biosimilar/Inflectra by Celltrion; Brazil proposing 'similar biologics' be treated as generics).**
  - **Demand: E.g., Brazil: mAb treatment use 1/3 of UK; 1/6 of USA: large potential channel.**
- ***"Success" of biosimilars***: dependent upon large generics, small generics, branded companies, and payors to **coordinate efforts**.
  - **Key: agreement on exclusivity, markets, promotion, and regulatory oversight.**

Overall

- Biologics have provided **incredible social benefits**.
- Costs are **high; biosimilars may address**.
- Biosimilar situation **like generic chemical drug era**.
- Global **biosimilars have significant risks and upside benefits**.
- Success will be dependent upon **technical, finance, and payor characteristics** in each particular market.